

Home haemodialysis in the Netherlands: State of the art

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ABSTRACT

Home haemodialysis (HHD) has gained popularity in recent years, due to improved clinical outcomes associated with frequent or prolonged haemodialysis sessions, best achievable at home. However, several barriers to HHD are perceived by the physician and patient, among which lack of experience and education, logistic difficulties and reimbursement issues seem to be the most important ones. HHD, in particular when performed with intensified frequency or duration, is associated with improved quality of life, blood pressure control and survival. Serious adverse events are rare; however, more vascular access complications arise due to frequent needling. This emphasises the importance of comprehensive education and training. This review aims to provide the physician with a detailed state of the art overview on HHD in the Netherlands, discussing potential barriers and benefits, and offering practical advice.

KEYWORDS

Barriers, daily haemodialysis, education, home haemodialysis, nocturnal haemodialysis

INTRODUCTION

In 1961 home haemodialysis (HHD) was introduced by the Japanese doctor Yukihiro Nosé.¹ The reason to perform haemodialysis (HD) in this unorthodox environment was primarily a practical consideration, since a proportion of the patients with end-stage renal disease (ESRD) could not be offered in-centre chronic haemodialysis due to capacity problems. The first HHD session was performed by a domestic washing machine with a frame coil dialyser, hence reducing costs. In the early 1960s, HHD programs were initiated in Seattle, Boston and London, and the rest of the world followed shortly thereafter.² In the Netherlands, the first patient was treated with HHD in 1968.³ In the early 1970s, 59% of the dialysis population in the United Kingdom and 32% in the USA received HHD. By the end of the 1970s the number of HHD patients reached its peak.⁴ Prevalence in Australia and New Zealand was as high as 45%.⁵ At that time, 10% of dialysis patients were treated with HHD in the Netherlands.⁶ Due to several factors, HHD rapidly waned from practice in the 1980s and 1990s, although large variations between countries remained. Australia and New Zealand maintained the largest population of HHD patients (9% and 18%, respectively),⁷ while prevalence of HHD in the USA declined to 2%⁸ and some countries no longer offered HHD at all.⁹ Reasons for the decrease in HHD in the Netherlands include the introduction of continuous ambulatory peritoneal dialysis in 1979,¹⁰ the

increase of living kidney transplantation, the formation of satellite HD facilities, and eventually, lack of experience of nephrologists.^{4,11}

Over the past decade, cumulative evidence demonstrated improved clinical outcomes with more frequent and/or prolonged (nocturnal) HD (in this paper designated by the term intensive HD), more easily provided in the home environment, compared with in-centre conventional HD (CHD). This, combined with the demand for reduction in healthcare costs, has led to a renewed interest in HHD. In the Netherlands, the number of HHD patients is steadily increasing from 112 (~2.0% of all dialysis patients) in 2006 to 273 patients (~4.2%) in 2016.¹² Probably, a lot more patients could benefit from this treatment modality. This narrative review aims to provide a thorough overview of current practices and literature on HHD.

PATIENT SELECTION, EDUCATION AND TRAINING

Patient selection

Whether a patient is suitable to perform HHD is largely dependent on patient motivation and the availability of family or medical staff support.^{13,14} In fact, most of the patients requiring dialysis are medically suitable for HHD.^{13,15,16} According to the National Institute for Health and Care Excellence (NICE), suitable candidates for HHD should be able and willing to learn the technique, be able to carry out the procedure (or be supported by a caregiver), be stable on dialysis, have suitable vascular access and have appropriate housing – after adaptations have been made – to accommodate the HD machine and equipment. Contraindications include severe intradialytic hypotension¹⁷ and unstable behavioural problems.^{17,18} The patient selection process, which includes providing information and a comprehensive assessment of the patient's healthcare needs and social circumstances including a home visit, should identify patients who are both physically and mentally able to perform HHD.

Patient education

The early identification of a potential HHD patient and timely initiation of patient education in the pre-dialysis period can help to overcome the barriers to HHD (see Barriers to home haemodialysis, later in this article). A comprehensive pre-dialysis education (CPE) program should provide patients and their family with clear and objective information on chronic kidney disease and the different treatment modalities, including kidney transplantation and conservative care. The program should promote self-care dialysis, use a multidisciplinary approach (nephrologist, dialysis nurse, dietician, psychologist, social worker), address psychosocial attitudes, misconceptions

and fears, and promote shared-decision making. Of utmost importance is a dedicated team, with expertise in different treatment modalities. CPE programs meeting these criteria are successful in increasing the number of patients choosing home dialysis, including HHD, even after an urgent unplanned start of dialysis.¹⁹⁻²¹ Shukla et al. reported on a successful CPE program in their clinic for future dialysis patients. The program required patients to attend a half-day at the clinic, starting with a whole-group session on kidney disease and renal replacement therapy options followed by individualised sessions with a dialysis nurse, a dietician, a social worker and the nephrologist. Patients were able to re-attend the program, yet almost 50% attended only one day prior to their first dialysis session. After multiple program meetings, the majority of 70% chose dialysis treatment at home: 55% chose peritoneal dialysis and 15% chose HHD.²¹ After initiation of the CPE program the number of home dialysis patients more than doubled.

Patient training

Initial HHD patient training is performed by a few training facilities in the Netherlands, since a centralised program facilitates logistics and optimises clinical expertise.²² The training comprises all aspects of HD, from preparation of the dialysis fluid to machine set-up, from access puncturing and access care to assessing dry weight, etc. The training program should train patients and family caregivers to act appropriately in case of acute events and instruct them to call the dialysis centre or hospital 24 hours a day for any acute problem. The training period generally lasts 6-12 weeks, subject to the patient's knowledge and skills.

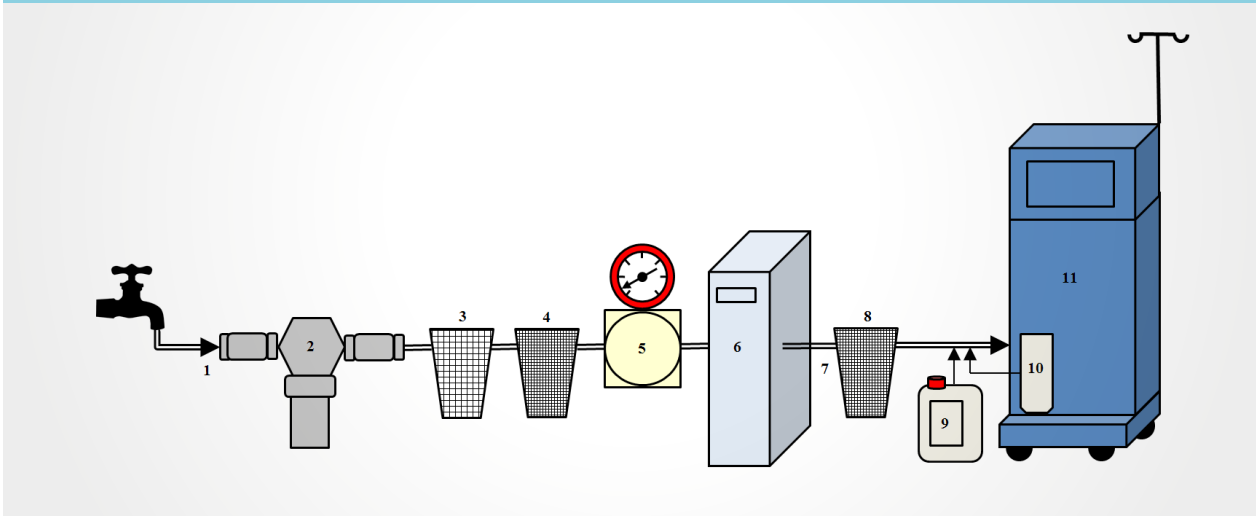
PRACTICAL AND TECHNICAL ISSUES

Not every house is suitable for HHD because it requires space, plumbing and electrical modifications to accommodate the dialysis machine, and will put higher demands on standard utilities and services.

Drinking water

The Water Supply Act in the Netherlands sets the standard for water used for drinking, cooking, and other domestic purposes.²³ With regard to public health, additional demands are imposed by the 'drinking water decree'.²⁴ The drinking water regulations establish the standards to be met by water supply companies concerning the design of facilities, control measures, and registration in logbooks.²⁵ The Dutch water supply companies are responsible for the delivery of drinking water that complies to the aforementioned obligations. Dutch drinking water is non-chlorinated and free of chloramines, in contrast to

Figure 1. Standard water treatment system for HHD in the Netherlands. 1: drinking water, 2: backflow preventer, 3: 30-micron sediment filter, 4: 5-micron sediment filter, 5: pressure meter, 6: RO unit, 7: purified or RO water, 8: extra filter, 9: acid concentrate, 10: bicarbonate concentrate, 11: haemodialysis machine



drinking water in many other countries where disinfection with chlorine is still utilised. Chlorine is harmful to reverse osmosis (RO) membranes in the dialysis machine, also chloramines are toxic to humans. In situations where dialysate was contaminated with chloramines, patients developed haemolytic anaemia and methaemoglobinemia.²⁶ If feed water contains chlorine and/or chloramines, an activated carbon filter is mandatory. Because of the non-chlorinated drinking water, activated carbon filters are not a standard feature in water treatment systems for HHD in the Netherlands.

Water treatment systems for HHD

Drinking water taken from the urban supply is not safe for use in HD. Drinking water enters the water treatment system through a backflow-preventing device (*figure 1*). This backflow preventer is installed to prevent pollution of the urban water supply infrastructure due to backflow of the domestic water system.²⁷

The drawn water passes two coarse filters to remove particulate matter, first a 30-micron sediment filter, then a 5-micron sediment filter. Next, the filtered water may be softened by a softener to protect the reverse osmosis membrane (RO membrane) from calcium and magnesium. The hardness of Dutch drinking water is low. Softeners are thus optional in Dutch domestic water treatment systems. The need for a softener is merely determined by the specifications of the portable RO unit used. Dependent of the brand and type, portable reverse osmosis units (RO units) require a water inlet pressure between 1.5 and 3.0 Bar. The water pressure in the Dutch urban water supply systems is sufficient to overcome the pressure reduction

by the domestic water treatment system. A booster pump is therefore not a standard feature of the water treatment system at home. Under special circumstances, such as positioning of the water treatment system on the ceiling, a booster pump is needed to provide a water pressure sufficient for normal functioning of the RO unit. The filtered (and softened) feed water is led into the portable RO unit for removal of ions, microbiological contaminants (bacteria, endotoxins, viruses) and dissolved organic substrates.

Water leaving the RO unit is called purified or RO water. The RO water is transported to the dialysis machine by a domestic distribution ring adapted to the specific situation on-site. The RO water passes one or two extra filters depending on the specifications of the dialysis machine used, hereby achieving additional bacterial, viral and endotoxin retention. The purified water is further processed into dialysate by adding acid concentrate and bicarbonate. RO water and dialysate for HHD should meet quality standards equal to those specified for in-centre HD as set by The Dutch Federation of Nephrology (in line with the European Pharmacopoeia Commission (*table 1*)).

Table 1. Microbiological requirements and endotoxin levels

	Micro-organisms, cfu/ml	Endotoxin, IU/ml
Tap water	On average 100	Not specified
Purified water	< 100	< 0.25
Dialysate	< 100	< 0.25

Electrical requirements

The current electrical safety norms, NEN1010:2015, were specified by Academic Hospitals Instrumentation Management Working Group (WIBAZ) in October 2015. NEN1010:2015 was incorporated in the Dutch Building Decree, which entered into force on 23 December 2016. HD is assigned to group 2. Safe HHD thus requires an isolation transformer.

Dialysis machines

Basically, all types of commercially available dialysis machines are suitable for HHD. Differences in design, size, noise level, user interface, and total cost of ownership will guide organisations enabling HHD to opt for a specific brand and type of dialysis machine. Over the last decade, several transportable HD machines have been introduced. They all have a short set-up time with disposable cartridges and automatic priming. These machines have a compact cyclor ($\pm 40 \times 40 \times 45$ cm) and make use of 5 litre lactate-based dialysate bags, or have the possibility to produce purified water themselves from the domestic water supply. Novel miniaturised HD machines are in development.

Quality control and maintenance

HHD quality control is organised in accordance with currently applicable clinical guidelines. Quality control includes calibration of the dialysis machine at home at the time of installation, quarterly examination of RO water and dialysate (on bacterial contamination and endotoxins), and a yearly check on the levels of organic and inorganic contaminants. Scheduled maintenance of water treatment systems and dialysis machines is mandatory. Specific mutual arrangements with water supply companies are necessary. Water supply companies should be informed about patients on HHD in their region and need to inform enablers of HHD timely in case of work on the urban water supply system or increased concentrations of toxic substances, such as aluminium.

Logistics

HHD patients need scheduled home delivery of materials and prescriptions related to dialysis. As a rule of thumb patients receive a four-week delivery, meaning shipment of a trolley containing one and a half to two cubic meters of materials. The materials are to be stored in patients' homes including an additional two-week stock in case of unforeseen events. Most HHD providers strive for a single supplier situation to prevent frequent deliveries by third parties.

Monitoring of treatment and patients

Monitoring of patients during HHD is an ongoing challenge. So far, monitoring of HHD is based on completed paper records, video calls using available non-secure commercial applications, and/or visits to the outpatient clinic. Initiatives to develop encrypted (safe) IT solutions allowing online monitoring during HHD and video calling and storage of the visual material are eagerly awaited.

HOME HAEMODIALYSIS REGIMENS

The dose of dialysis delivered with CHD is often limited by the overall weekly treatment time and frequency. To deliver the minimum amount of adequate dialysis, CHD utilises high-efficiency dialysis over a short period of time. The resulting peaks and troughs of both hydration status and uraemic retention solute concentrations can lead to dramatic changes in the internal milieu. The home setting offers more flexibility of treatment schedule and facilitates intensive HD sessions, which are summarised in *table 2*.²⁸ Intensive HD regimens include short daily haemodialysis (SDHD), prolonged and prolonged-frequent HD. Prolonged (frequent) HD is usually performed during the night (nocturnal HD). Intensive HD can reduce the fluctuations of the internal environment by maintaining a more steady state, and by avoidance of a long interdialytic interval.²⁹

Table 2. Conventional and intensive haemodialysis regimens (Adopted from Chan CT et al.²⁸)

	Conventional HD	SDHD (frequent)	Prolonged HD	Prolonged – frequent HD
Frequency (times/week)	3	5-6	3-4	5-6
Duration (hours/session)	4	2-3.5	> 5.5	> 5.5
Dialysate flow (ml/min)	500-800	500-800	300-500	300-500
Blood flow (ml/min)	300-400	400	200-400	200-300
Standardised Kt/V _{urea}	2.5 (12h/week)	3.75 (13.5h/week)	3.75 (26.8h/week)	5.82 (40.2h/week)

HD = haemodialysis; SDHD = short daily HD.

OUTCOMES OF HOME HAEMODIALYSIS

Patient survival

HHD has undergone a significant revival during the past 10 years.³⁰ Growing data supporting the association of intensive HD, most easily achieved in the home setting, with improved outcomes such as survival are the primary drivers for this resurgence. Most survival studies did not compare HHD versus in-centre HD, but intensive regimens (mostly performed at home) with a conventional (3x/week) regimen. Charra et al. reported a dramatic improvement in survival of dialysis patients in Tassin (France) by extending the length of HD sessions.³¹ The survival benefit for patients undergoing nocturnal (NHD) and short-daily (SDHD) haemodialysis has been evaluated in a number of studies. Although no well-powered randomised controlled trial has been performed to date and the bulk of the data remain observational, the evidence points toward a better survival for patients receiving SDHD and NHD compared with those treated with conventional regimens.³²⁻⁴¹ A cohort study by Lacson et al. reported a mortality benefit for in-centre nocturnal HD (INHD) with a significant hazard ratio (HR) at both 1 year (HR 0.73, 95% CI 0.56-0.96, $p = 0.02$) and at 2 years (HR 0.75, 95% CI 0.61-0.91, $p = 0.004$) compared with a propensity-score-matched in-centre CHD arm.⁴⁰ Ok et al. also demonstrated a one-year survival advantage favouring INHD over CHD (HR 0.32, 95% CI 0.10-0.98, $p = 0.04$) after adjusting for age, gender, dialysis vintage, and the presence of diabetes.⁴¹ In a study of prevalent Canadian patients, Pauly et al. reported a five-year survival rate of 85% among patients receiving nocturnal HHD (NHHD), a rate comparable with that of patients who had received a deceased donor transplant in the USA.⁴² The Frequent Hemodialysis Network (FHN) Nocturnal Trial, randomising dialysis patients to either CHD (home or in-centre) or NHHD (six times a week), did not find a significant effect of NHHD on outcome.⁴³ The lack of differences in the latter trial is likely due to the small number of patients enrolled, an increased number of incident uraemic patients enrolled (> 50%) whose residual kidney function could likely have blunted the beneficial effects of the frequent dialysis, a remarkably low mortality rate in the CHD group, and the fact that one-third of the NHHD patients were less adherent to the treatment with less than 80% of the prescribed dialysis sessions done. Johansen et al. compared intensive (both nocturnal and frequent) HHD with in-centre CHD, using propensity score matching, and reported an HR of 0.36 (95% CI 0.22-0.61) for death, favouring NHHD. SDHD was not associated with a survival advantage (HR 0.64, 95% CI 0.31-1.31).³⁸ The FHN Daily Trial, randomising dialysis patients to in-centre SDHD (six times a week) or in-centre CHD, found a survival benefit in the SDHD treatment group.⁴⁴ A recent observational study in a large

cohort of Canadian HHD patients did not find a reduction in the relative risk for the composite of death and treatment failure in patients treated with either NHHD or SDHD, after multivariable adjustment for patient and centre factors (e.g. vascular access type), compared with home CHD (NHHD: HR 0.83, 95% CI 0.66-1.03; SDHD: HR 0.84, 95% CI 0.63-1.12).⁴⁵ This could be explained by low mortality rates in all home dialysis groups. Although this study did not demonstrate a benefit of dialysis intensity, potential advantages of treatment in the home environment could not be studied due to the lack of an in-centre treatment group.

Summarising, evidence is growing for improved survival from intensive forms of haemodialysis (frequently but not invariably performed at home), as compared with conventional HD (mostly performed in-centre).

Blood pressure

Blood pressure (BP) control is one of the most consistent benefits of intensive HD in randomised and non-randomised studies.^{43,46-51} One of the first reports of improved BP control in intensive HD came from France, where mean ambulatory BP was shown to be inversely correlated with HD session duration.⁵² Subsequently, the FHN study showed a significant reduction in systolic BP of -9.7 mmHg (range from -16.9 to -2.5) during 12 months of follow-up in the NHHD cohort, with a significant decrease in the number of antihypertensive agents.⁴³ The lack of significant difference in BP readings in patients on a CHD prescription (4 hours, 3 times a week) although performed in the home setting, illustrated the importance of intensive HD as opposed to location of HD delivery as the main factor driving BP control. NHD reduces BP by lowering of total peripheral resistance and plasma norepinephrine levels.^{49,50} Another factor leading to improved BP control is improved fluid balance, as achieved by SDHD.⁴⁸

Cardiac indices

Evidence from studies with SDHD^{44,48,53} and N(H) HD^{46,48,54} demonstrated that intensive HD is associated with improvements in left ventricular mass index and left ventricular hypertrophy, which are factors associated with cardiovascular morbidity and mortality in dialysis patients including heart failure and sudden arrhythmic death.⁵⁵ These findings are confirmed by a recent meta-analysis of observational studies and data from RCTs that reported improvement in left ventricular mass index and geometry in both frequent and prolonged HD groups.⁵⁶ Furthermore, a cross-sectional study demonstrated that intensive HD regimens (home or in-centre) were associated with a significant reduction in intradialytic systolic hypotension and dialysis-induced myocardial stunning compared with in-centre CHD.⁵⁷ A Dutch randomised cross-over study recently confirmed improvement of haemodynamic

(peripheral systolic, peripheral diastolic and central BP) and cardiac stability, associated with better preservation of relative blood volume, during prolonged haemodialysis sessions as compared with CHD sessions.⁵⁸ Finally, two retrospective observational Canadian studies showed that frequent NHHD is associated with improvement of electrocardiographic features linked to sudden cardiac death.^{59,60}

Elimination of the long (2-day) interdialytic interval over the weekend, inherent to a thrice-weekly dialysis regimen, may be an important factor in reducing cardiovascular risk with intensive HD since fluid overload and metabolic derangements (e.g. hyperkalaemia) are more pronounced after the long interdialytic interval and may lead to cardiovascular events and mortality.⁶¹⁻⁶³ Evidence from retrospective observational studies with in-centre CHD suggest that myocardial infarction, dysrhythmia, heart failure, stroke and all-cause mortality (including sudden and cardiac death) are higher on the day after the long interdialytic interval than during any other day of the week.⁶⁴⁻⁶⁹ This pattern was not observed in patients receiving in-centre CHD > 3x/week, HHD (~70% performed dialysis thrice weekly for > 4 h per session and ~20% > 3x/week) or peritoneal dialysis.⁶⁵ However, an observational cohort study using the US Renal Data System did not find a reduced risk of arrhythmia-related hospital admissions for daily HHD patients as compared with matched in-centre CHD patients. Of note, the risk of heart failure-related admission was ~40% lower.⁷⁰ Prospective, preferably randomised, trials are required to determine whether intensive (H)HD reduces sudden cardiac death, cardiovascular morbidity and mortality in HD patients.

Bone mineral metabolism

The cumulative evidence points towards improved management of bone mineral abnormalities by the use of intensive HD.^{43,56,71} It is common for patients on intensive HD prescriptions to require fewer phosphate binders, and they frequently need phosphate supplementation in the dialysate.⁷² In the long term, improved control of hyperphosphataemia and secondary hyperparathyroidism by intensive HD may translate into significant risk reduction of vascular calcification, potentially contributing to increased survival in this dialysis population. Up to now, data regarding vascular calcification in HHD are inconclusive.⁷³

Anaemia control

Normochromic (renal) anaemia and iron deficiency anaemia are extremely common in the dialysis population.⁷⁴ It is unknown whether intensive (H)HD has a direct effect on haemoglobin levels or erythropoietin resistance. In observational studies in HHD increased haemoglobin levels were found after intensified

treatment.⁷⁵⁻⁷⁷ Yet, an RCT did not find a difference in haemoglobin levels or erythropoietin-to-haematocrit ratio between intensive HD and CHD.⁵⁴ Evidence from observational studies suggests that erythropoiesis-stimulating agent requirement seems to decrease with intensive home treatment,^{76,77} even in comparison with a propensity-score-matched in-centre CHD arm.⁷⁸ However, in the FHN nocturnal trial, erythropoietin dosage was not different between the NHHD and the CHD treatment arm.⁴³

Iron supplementation is favoured in the form of intravenous iron, as a better effect on haemoglobin levels is expected.⁷⁹ However, intravenous iron administration at home is controversial, as serious adverse events (e.g. anaphylactic reactions) might occur.⁸⁰ This might be a logistic barrier to perform HHD. The Dutch Federation of Nephrology has therefore developed a practical standard for intravenous iron administration at home. Recommendations include administration of a limited amount (maximal 100 mg each time) of non-dextran iron (less known for adverse events) in no less than 30 minutes, by trained patients or nurses with uncomplicated single administration in a centre as prerequisite.⁸¹

Pregnancy outcomes

Another important benefit of intensive HD is its effect on fertility. Conception rates and pregnancy outcomes are overall poor in patients on dialysis. There are emerging observational data from patients on intensive HD with lower urea levels that show significantly better pregnancy outcomes compared with CHD.⁸²⁻⁸⁵ It is thought that the increased rates of successful conception observed in child-bearing age female ESRD patients receiving intensive HD may be partially due to restoration of the pituitary-hypothalamic axis augmented by improved solute clearance. At the same time, improved clearance (lower urea levels), fluid balance, BP control and haemodynamic stability in intensive HD, could positively impact on pregnancy outcomes.^{85,86} In the male population, intensive HD (NHHD) could also improve fertility, possibly by an increase in testosterone levels and decreasing hyperprolactinaemia.⁸⁷

Quality of life

The impact of home intensive HD on quality of life (QoL) has been the subject of multiple studies, and overall results show an increase in kidney-specific domains of QoL parameters.^{47,54,88-91} This increase in QoL with intensive HD regimes may be due to increased autonomy and functionality, reduced pill burden, liberalisation of dietary restrictions and fluid intake, considerable reduction in the time spent in the hospital and in transit to and from the hospital, optimised employment (productivity), and a reduction of inflammation and uraemic symptoms.

NHHD has been shown to be associated with mood improvement, an important domain of QoL associated with improved outcomes.⁵⁴ This might be due to improved sleep quality due to a reduction in sleep apnoea with NHHD. The FREEDOM study showed a reduction in the prevalence of restless legs syndrome from 35 to 26% after 12 months of home SDHD ($p = 0.05$),⁹² while NHHD has been associated with a reduction in the frequency of sleep apnoea episodes.⁹³

VASCULAR ACCESS

Type of access

A well-functioning vascular access is of crucial importance for safe and long-lasting HHD. According to the European Best Practice Guideline on vascular access,⁹⁴ an autogenous arteriovenous (AV) fistula is the vascular access of choice in all HD patients. As fear of self-cannulation is the most frequently reported barrier in HHD,⁹⁵ a central venous catheter (CVC) might be considered to be a suitable type of access for HHD. However, in the in-centre HD population CVC use has been associated with a higher risk of death.⁹⁶ Of course, this could be explained by differences in patient type between patients with an AV fistula vs. CVC (confounding by indication). However, equivalent results can be found in recent literature in the NHHD and HHD population: patients with CVC treated at home have a higher mortality risk compared with patients with an AV access,⁹⁷ even in a propensity-matched cohort.⁹⁸ In addition, using a CVC was associated with a higher risk for hospitalisation and local infections.^{98,99} Overall, AV fistulas are the first choice and AV prosthetic grafts are preferred over CVCs.⁹⁴ CVCs should be reserved for a select group of patients with severe artery disease, severe heart failure, malignancy or anticipated short time to kidney transplantation. Also in elderly patients with limited life expectancy, a CVC might be an acceptable choice.^{100,101}

Self-cannulation and buttonhole vs. rope ladder technique

HHD patients performing self-cannulation obtain the highest possible independency. In the Netherlands, patients are trained in less than three weeks with the 'Tandem-hand' cannulation: the first week the nurse inserts the needle under physical guidance of the patient, the next week the patient inserts the needle with physical guidance of the nurse, the last week the patient performs the cannulation by himself in the nurse's presence.¹⁰² The buttonhole technique, or constant site technique, was first described in 1977.¹⁰³ Due to repeated insertion of the needle at exactly the same site and in the same angle, in 2-3 weeks' time a tunnel of fibrous tissue is formed allowing successive insertion with blunt needles. In daily practice, the buttonhole technique is frequently used in

patients with fear of self-cannulation since this technique is believed to be less painful. Yet in the HHD literature no significant effect on cannulation pain was found with the buttonhole technique,¹⁰⁴ although this study is likely biased since it included a selection of patients experiencing painful cannulation. A definitive advantage is improved survival of AV fistulas, including a reduction of aneurysm formation and reduced need of access interventions, with buttonhole instead of the rope ladder technique.¹⁰⁵⁻¹⁰⁷ The biggest concern with buttonhole remains the risk of infections: in a systematic review more infections were found in the buttonhole group compared with rope ladder cannulation (combined RR 3.18, 95% CI 2.12-4.77).¹⁰⁸ In conclusion, rope ladder is the preferred method for cannulation. Yet, in patients with a short fistula and fear of self-cannulation, buttonhole remains a possible alternative if preventive hygiene is strictly followed.¹⁰⁹

Surveillance

In HD in general, recommendations for access surveillance comprise access flow measurement at least every month in AV grafts and every 3 months in AV fistulas,^{94,110} and there is no reason to deviate from these recommendations in HHD. Frequent monitoring reduces the risk of thrombosis formation.¹¹¹ As a routine measure, physical examination prior to any cannulation is recommended in order to identify possible access problems. Patients should be taught how to recognise infections, aneurysm and stenosis and they might benefit from retraining programs.^{22,112} The 'Arm Raise Technique' is an easy tool used to detect a possible stenosis.¹¹³ The biggest challenge in HHD is to incorporate frequent monitoring in the home environment. In some HHD centres, patients are invited to perform in-centre HD once every 2-3 months, in order to perform the access flow measurements. In the Netherlands, access flow measurements are executed at home (personal communication).

Access failure and infections

As previously described, HHD presents many advantages above in-centre CHD, but has possible additional complications.

In the FHN trials, *the time to first access event* (the composite of vascular access associated hospitalisation, repair and loss) was shorter with SDHD and NHHD compared with CHD (HR 1.76, 95% CI 1.11-2.79 and HR 1.81, 95% CI 0.94-3.48, respectively).¹¹⁴ Of note, buttonhole was associated with a longer complication-free period in comparison to the rope ladder technique. In the separate (underpowered) FHN studies, vascular access events were seen more frequently during follow-up, yet this was not significant (Daily trial HR 1.35, 95% CI 0.84-2.18 ($n = 245$)⁴⁴; Nocturnal trial HR 1.62, 95% CI 0.91-2.87 ($n = 87$)⁴³). Most importantly, the access

failure rate (single outcome) in NHHD and SDHD was comparable with in-centre CHD.^{43,114} We suggest that double needling might be associated with higher repair risks in these trials on frequent dialysis, yet no studies are available comparing complications in single-access needling (often performed in frequent NHHD in the Netherlands) and double-access needling. A well-founded advice on single versus double needling can therefore not be given. As expected, access failure is dependent on vascular access type: an access failure rate of 0.02-0.16/patient-years was reported in patients using an AV fistula or graft, whereas the rate in patients with a CVC was higher: 0.48-1.07/patient-years.^{99,114-120}

The event rate of thrombolysis in HHD ranged from 0.27-1.60/patient-years in patients using CVC. In patients using an AV fistula no thrombosis was seen during a follow-up of 6 months.¹²¹ Due to less exposure to pathogens in hospitals, patients on HHD are believed to be less susceptible to infections. Yet, patients treated with intensive HHD (5-6 sessions weekly) were hospitalised for infection more frequently than in-centre CHD patients.⁷⁰ Possible explanations for this finding include frequent use of the buttonhole technique, mediocre preventive hygiene, and an association with frequent dialysis. Patients performing NHHD and using the buttonhole technique were three times more likely to develop a vascular access-related sepsis than patients performing CHD.¹¹⁶

OTHER COMPLICATIONS

There is a lack of data comparing HHD events to in-centre dialysis events. Tennankore et al. report the occurrence of technical adverse events and severe events requiring intervention at a rate of 0.16 and 0.038 per 1000 dialysis sessions in a cohort of HHD patients dialysing a median of 5 times a week and 8 hours a session.¹²² The study by Wong et al. described a life-threatening event rate of only 0.060 per 1000 dialysis sessions.¹²³ Thus, current literature indicates that the overall event rates for these complications are acceptably low, which confirms the safety of HHD, but the potential for life-threatening events warrants discussion.^{49,124} These specific complications relate to three main areas: 1) dialysis techniques; 2) medical factors; and 3) psychosocial aspects.¹²⁵

Examples of errors in dialysis techniques include machine dysfunction, misuse of dialysis line set, inadequate preparation or contamination of water, and dialysis composition. To prevent technical complications, an adequate education and retraining program for the patient and/or dialysis partner is essential, in addition to accurate protocols and a staff member available 24 hours a day. It is also important to maintain patient awareness of the necessity of these safety protocols.

Successful HHD requires reliable vascular access. Most of the described medical events arose due to AV fistula or graft cannulation needle dislodgements, which were clearly related to patient error or equipment malfunction.¹²² An unobserved major bleed due to needle dislodgement during nocturnal dialysis is an important possible medical complication. Nevertheless, this risk can be reduced by securing the needles or the CVC with adhesive plasters and by using detector alarms to indicate blood loss. However, in the study by Tennankore, half the patients were not using the offered detector at the time of the event. In the case of nocturnal dialysis, it is possible to reduce this risk by using one needle, with still superior dialysis efficiency compared with a conventional regimen. A few reports address air embolism in the home setting, the majority of which were related to patient error.^{122,123}

Other possible medical complications of HD, including HHD, are hypotensive collapse or cardiovascular instability. However, intensive HHD is also known to be more effective for attaining cardiovascular balance. The safety of NHHD is enhanced by decreasing the ultrafiltration, blood flow and dialysate flow rates. Finally, the medical team should be alert to nutritional deficiencies, especially with regard to phosphate and the water-soluble vitamins. Despite the fact that these vitamins are supplemented after each HD session, we have identified substantial vitamin C deficiency in a significant number of our patients, especially those on intensive HD. Phosphate can be added to the dialysate in the form of phosphate enemas.⁷²

Psychosocial complications are often underestimated, but they influence the endurance of the HHD patient and/or partner.¹²⁵ Long-term treatment could lead to anxiety, depression and fatigue because of the perceived 'gloomy future' and the demands placed on the patient in terms of time and effort. This may lead to non-compliance and treatment failure. Therefore, psychosocial support is needed before and during the treatment period and the medical team should remain focused on these possible problems.

Thus, several reasons can explain treatment failure in HHD. Recent cohort studies determined that 18-25% of patients discontinued HHD treatment within the first year. Human error is the most common factor contributing to complications arising in the home setting, and usually results from not adhering to prescribed protocols. A high quality and successful HHD program must focus on minimising possible complications, improving event reporting and providing retraining. Therefore, it is important that a dialysis centre offering this modality is experienced in HHD and that patients and staff are trained to detect complications at an early stage. Emergency care for major events should be optimised and in-centre dialysis should be available to patients who fail in HHD. If these

factors are considered, the risks for complications are minimal.

BARRIERS TO HOME HAEMODIALYSIS

Despite the benefits of HHD compared with in-centre HD, the majority of dialysis patients (82%) in the Netherlands are treated in-centre with CHD. Both physician- and patient-perceived barriers prevent patients from adopting HHD. Physician attitudes towards HHD are positive. Surveys among nephrologists indicate that there is a strong belief in the benefits of intensive HD and that home is considered the best location for dialysis.¹²⁶⁻¹³⁰ The estimated percentage of patients considered medically and psychosocially fit to perform home dialysis ranges from 15 to 25%,^{13,18} which exceeds the current proportion of HHD patients in most countries by far. Physician-perceived barriers may, at least in part, explain the discrepancy between physicians' beliefs in HHD and current practice patterns. The perceived lack of patient motivation is one of the most frequently cited reasons not to start HHD,^{126,131,132} and may be related to suboptimal pre-dialysis patient education programs. Other commonly reported barriers are related to patient characteristics (e.g. age, comorbidities, cognitive impairment, socioeconomic disadvantages), complexity of the dialysis procedure, limited infrastructure (e.g. lack of training facilities), lack of dedicated resources (e.g. multidisciplinary team to educate and support HHD patients), and lack of expertise by nephrologists.^{126,133} The increased number of vascular access events in nocturnal HHD patients who perform self-cannulation may also play a role.⁴³ Other concerns are related to the costs of HHD. In the Netherlands, health insurers offer standard reimbursement rates for in-centre HD and HHD. This system is a disincentive to dialysis centres supporting patients on more intensive dialysis schedules and providing assistance by a home dialysis nurse, which are accompanied by higher actual costs compared with self-supported home CHD. This could be counteracted by accurate knowledge of the actual costs followed by offering more differentiated reimbursement rates by healthcare providers, more closely related to the actual costs of dialysis care. The DOMESTICO (Dutch nocturnal and home dialysis Study To Improve Clinical Outcomes) study group aims to conduct a large cohort study including home dialysis patients, to map actual costs of home dialysis, study examples of good practice and overcome barriers.

From a patient perspective, reasons not to opt for HHD are related to fears and the burden of undertaking HHD. The major barriers perceived by in-centre HD patients are lack of explanation of self-care dialysis, fear of self-cannulation, fear of a catastrophic event in the absence of medical staff support, the burden placed on

family caregivers, lack of self-confidence and/or self-efficacy in performing dialysis at home and a coinciding fear of receiving substandard care.¹³⁴⁻¹³⁷ Other reported barriers are a belief that patients should be supervised by medical staff, fear of social isolation, interference of treatment with home life, reluctance to perform the required home adaptations and insufficient space to store equipment and supplies.^{136,137} Physician and patient perceived barriers have to be overcome to expand HHD practice. Motivation and education of both patients and staff is essential to achieve this.^{138,139} Specialised training in HHD for nephrologists will create awareness of the benefits of this modality and encourage them to offer this treatment to patients. The characteristics and effectivity of a CPE program were addressed in the paragraph 'Patient education'. When patients opt for HHD, a patient-tailored plan should be drawn up. Allowing and encouraging patients to perform HHD independently of a family caregiver may enable more patients to adopt HHD and decrease the perceived burden on family members. Experiences from the UK and Finland show that solo-dialysis is feasible for the vast majority of HHD patients.¹⁴⁰ The support of a skilled home dialysis nurse may facilitate HHD in the absence of a family caregiver, in the case of debilitated patients or the elderly, who are now often considered poor candidates for HHD, and for patients with a CVC.^{141,142} Staff-assisted HHD eliminates the need for patient training and can be initiated immediately after installation of the equipment at home. It increases the patient's confidence in HHD and motivates patients to take responsibility and start a training program for self-supported HHD. The experience of a Dutch dialysis unit with 10 years of staff-assisted HHD shows that 30% of the patients starting with staff-assisted HHD can be converted to solo-dialysis or family-supported HHD (personal communication). Also, a hybrid of staff-assisted HHD and self-assisted HHD can be applied. For instance, when a patient and partner are afraid of self-puncturing, but can be responsible for the dialysis procedure, a skilled dialysis nurse can simply do the puncturing for them. Last, the design of less complex HHD devices requiring less storage space and less home modifications and the application of remote monitoring technology^{143,144} may improve patients' confidence to perform dialysis independently and effectively without direct supervision of medical staff, and in addition may shorten time of HHD training programs and lower the costs.

NEW DEVELOPMENTS

The increased popularity of HHD has stimulated the development of less complex, transportable (24-34 kg) and more user-friendly dialysis machines (see dialysis machines).^{145,146} All of these machines are low-dialysate-

flow systems (max 300 ml/min) requiring an increased time on therapy (typical treatment scheme: 4-6 times per week 2.5-4 hours). In the near future the release of a new compact (45 x 37 x 48 cm) cartridge-based dialysis machine of 29 kg suitable for HHD is expected (not yet FDA approved or CE certified).¹⁴⁷ The device needs a domestic water treatment system, but dialysate flow rates up to 500 ml/min can be applied.

The weight of the transportable HD machines is still considerable (≥ 24 kg) and all systems rely on conventional technology using pre-mixed or in-situ mixed dialysate (≥ 20 litres per treatment) in a single pass configuration. Continuous regeneration and reuse of a small amount of dialysis fluid in a closed-loop system renders the system independent of a large dialysate supply and allows further miniaturisation, but the technology is challenging. Currently, a portable artificial kidney of ~10 kg using ~6 litres of dialysate, is being developed by a collaborative effort of the Dutch Kidney Foundation and several biotechnology companies, based on the REDY (REcirculation DialYsis) technology combining adsorbent, ion exchange and enzyme techniques.¹⁴⁸ The device will be designed for every-other-day HHD. A functional model became available in 2016 and a first in-human clinical trial is expected to start in 2019. Other companies are working on comparable sorbent HD systems.¹⁴⁹⁻¹⁵⁰ In the meantime, initiatives towards further reducing the dimensions to wearable proportions, allowing maximum flexibility for the patient, are ongoing. One of the major challenges is urea removal since direct adsorption of urea is very difficult while a relatively large amount needs to be removed daily (around 400 mmol \approx 25 grams).¹⁵¹ A wearable artificial kidney of 5 kg relying on urease (as the REDY technology) has been designed. Urease is an enzyme that catalyses hydrolysis of urea to carbon dioxide/bicarbonate and ammonia/ammonium. The device was successfully tested in a first-in-human trial during 24 hours (FDA fast track status).¹⁵² However, removal of ammonium, which is more toxic than urea, requires extra sorbent (zirconium phosphate) and solutes (i.e. concentrated infusate with cations removed by zirconium phosphate and sodium bicarbonate to neutralise protons released in exchange for ammonium) which limits further miniaturisation. Initiatives to develop alternative urea removal strategies allowing further miniaturisation to truly wearable proportions (< 1.5 kg) such as direct adsorption¹⁵³ and electrochemical urea degradation¹⁵⁴ are ongoing but still far from clinical application.

Another development in the field of HHD is the application of remote telemonitoring systems to record patient- and treatment-related parameters and allow for (face-to-face) communication.^{155,156} This could reduce patients' experiences of social isolation and anxiety about the absence of medical staff, reduce travel time and enable

health professionals to monitor treatment and compliance more continuously, advise patients on how to adjust their treatment themselves, and facilitate remote assistance in case of acute problems.

The Dutch Kidney Foundation is supporting some of these new developments, and also stimulates the different forms of home dialysis by the recent initiation of a Taskforce Home Dialysis.

CONCLUSION

It is difficult to make practice recommendations regarding HHD based on the current body of evidence. There is a lack of large RCTs, which are not feasible to perform. Well-matched prospective cohort studies on a broader range of outcomes (e.g. quality of life, hospitalisations, vascular access associated complications, blood pressure control) are needed to provide greater certainty about the clinical benefits of HHD. However, current evidence indicates that intensive HD, facilitated in the home setting, is associated with improved clinical outcomes at the expense of more vascular access complications. Although severe and life-threatening events rarely occur in HHD, strict regulations combined with patient education and retraining on technical issues, preventive hygiene and emergency situations are important. In order to provide a high level of care, in both knowledge and logistics, a dedicated and experienced team is needed. National initiatives to promote learning between centralised dialysis facilities and regional centres are currently in development in the Netherlands.

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REFERENCES

1. Nose Y. Home hemodialysis: a crazy idea in 1963; a memoir. *ASAIO J.* 2000;46:13-7.
2. Blagg CR. Home haemodialysis: 'home, home, sweet, sweet home!' *Nephrology (Carlton)*. 2005;10:206-14.
3. Dianet (cited 1 November 2017). Available from: <https://www.dianet.nl/over%20dianet/organisatie/geschiedenis>.
4. Agar JW. International variations and trends in home hemodialysis. *Adv Chronic Kidney Dis.* 2009;16:205-14.

5. ANZDATA Registry. 2nd Report of the Australia and New Zealand Dialysis and Transplant Registry [Internet]. 1979 [cited 10 August 2017]. Available from: <http://www.anzdata.org.au>
6. Renine-database, stichting Nefrovisie.
7. ANZDATA Registry. 39th Report, Chapter 6: Home Dialysis. Australia and New Zealand Dialysis and Transplant Registry, Adelaide, Australia. 2016. Available from: <http://www.anzdata.org.au>.
8. United States Renal Data System. 2016 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2016.
9. European Renal Association – European Dialysis and Transplantation Association Annual Report 2015 (EDTA) Registry [Internet]. 2015 (cited august 10 2017). Available from: <https://www.era-edta-reg.org>
10. Boeschoten EW, Krediet RT, Arisz L, et al. A new method of kidney function substitution treatment: continuous ambulatory peritoneal dialysis. *Ned Tijdschr Geneesk*. 1980;124:461-4.
11. Blagg C. What Went Wrong with Home Hemodialysis in the United States and What Can Be Done Now? *Hemodial Int*. 2000;4:55-8.
12. Nefrodata, Dutch Federation of Nephrology (NFN). (cited 20 July 2017). Available from: <https://ivisualz.nl/ivisualz/chartFlash/charts>
13. Moran J, Kraus M. Starting a home hemodialysis program. *Semin Dial*. 2007;20:35-9.
14. Rioux JP, Marshall MR, Faratro R, Hakim R, Simmonds R, Chan CT. Patient selection and training for home hemodialysis. *Hemodial Int*. 2015;19 Suppl 1:S71-S79.
15. Jayanti A, Foden P, Mitra S. Multidisciplinary staff attitudes to home haemodialysis therapy. *Clin Kidney J*. 2017;10:269-75.
16. De Maar JS, de Groot MA, Luik PT, Mui KW, Hagen EC. GUIDE, a structured pre-dialysis programme that increases the use of home dialysis. *Clin Kidney J*. 2016;9:826-32.
17. Kuipers J, Oosterhuis JK, Krijnen WP, et al. Prevalence of intradialytic hypotension, clinical symptoms and nursing interventions--a three-months, prospective study of 3818 haemodialysis sessions. *BMC Nephrol*. 2016;17:21.
18. Technology Appraisal Guideline No 48; Guidance on home compared with hospital hemodialysis for patients with end-stage renal failure. London: National Institute for Clinical Excellence (NICE), 2002. (cited 30 August 2017). Available from: http://www.nice.org.uk/nicemedia/pdf/HvH_full_guidance.pdf
19. Goovaerts T, Jadoul M, Goffin E. Influence of a pre-dialysis education programme (PDEP) on the mode of renal replacement therapy. *Nephrol Dial Transplant*. 2005;20:1842-7.
20. Rioux JP, Cheema H, Bargman JM, Watson D, Chan CT. Effect of an in-hospital chronic kidney disease education program among patients with unplanned urgent-start dialysis. *Clin J Am Soc Nephrol*. 2011;6:799-804.
21. Shukla AM, Easom A, Singh M, et al. Effects of a comprehensive predialysis education program on the home dialysis therapies: a retrospective cohort study. *Perit Dial Int*. 2017;37:542-7.
22. Young BA, Chan C, Blagg C, et al. How to overcome barriers and establish a successful home HD program. *Clin J Am Soc Nephrol*. 2012;7:2023-32.
23. Act on water supply (Drinkwaterwet), BWBR0026338, entered into force on 1 July 2015.
24. Drinking water decree (Drinkwaterbesluit), BWBR0030111 entered into force on 28 November 2015.
25. Drinking water arrangement (Drinkwaterregeling), BWBR0030152, entered into force 20 July 2017.
26. Perez-Garcia R, Rodriguez-Benitez P. Chloramine, a sneaky contaminant of dialysate. *Nephrol Dial Transplant*. 1999;14:2579-82.
27. Ahmad S. Essentials of water treatment in hemodialysis. *Hemodial Int*. 2005;9:127-34.
28. Chan CT, Covic A, Craig JC, et al. Novel techniques and innovation in blood purification: a clinical update from *Kidney Disease: Improving Global Outcomes*. *Kidney Int*. 2013;83:359-71.
29. Perl J, Chan CT. Home hemodialysis, daily hemodialysis, and nocturnal hemodialysis: Core Curriculum 2009. *Am J Kidney Dis*. 2009;54:1171-84.
30. George CR. History of home haemodialysis in Australia. *Nephrology (Carlton)*. 2005;10:215-21.
31. Charra B, Caemard E, Ruffet M, et al. Survival as an index of adequacy of dialysis. *Kidney Int*. 1992;41:1286-91.
32. Kjellstrand C, Buoncristiani U, Ting G, et al. Survival with short-daily hemodialysis: association of time, site, and dose of dialysis. *Hemodial Int*. 2010;14:464-70.
33. Jun M, Jardine MJ, Gray N, et al. Outcomes of extended-hours hemodialysis performed predominantly at home. *Am J Kidney Dis*. 2013;61:247-53.
34. Pauly RP, Maximova K, Coppens J, et al. Patient and technique survival among a Canadian multicenter nocturnal home hemodialysis cohort. *Clin J Am Soc Nephrol*. 2010;5:1815-20.
35. Blagg CR, Kjellstrand CM, Ting GO, Young BA. Comparison of survival between short-daily hemodialysis and conventional hemodialysis using the standardized mortality ratio. *Hemodial Int*. 2006;10:371-4.
36. Weinhandl ED, Liu J, Gilbertson DT, Arneson TJ, Collins AJ. Survival in daily home hemodialysis and matched thrice-weekly in-center hemodialysis patients. *J Am Soc Nephrol*. 2012;23:895-904.
37. Nesrallah GE, Lindsay RM, Cuerden MS, et al. Intensive hemodialysis associates with improved survival compared with conventional hemodialysis. *J Am Soc Nephrol*. 2012;23:696-705.
38. Johansen KL, Zhang R, Huang Y, et al. Survival and hospitalization among patients using nocturnal and short daily compared to conventional hemodialysis: a USRDS study. *Kidney Int*. 2009;76:984-90.
39. Lockridge RS, Kjellstrand CM. Nightly home hemodialysis: outcome and factors associated with survival. *Hemodial Int*. 2011;15:211-8.
40. Lacson E Jr, Xu J, Suri RS, et al. Survival with three-times weekly in-center nocturnal versus conventional hemodialysis. *J Am Soc Nephrol*. 2012;23:687-95.
41. Ok E, Duman S, Asci G, et al. Comparison of 4- and 8-h dialysis sessions in thrice-weekly in-centre haemodialysis: a prospective, case-controlled study. *Nephrol Dial Transplant*. 2011;26:1287-96.
42. Pauly RP, Gill JS, Rose CL, et al. Survival among nocturnal home haemodialysis patients compared to kidney transplant recipients. *Nephrol Dial Transplant*. 2009;24:2915-9.
43. Rocco MV, Lockridge RS, Jr., Beck GJ, et al. The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. *Kidney Int*. 2011;80:1080-91.
44. Chertow GM, Levin NW, Beck GJ, et al. In-center hemodialysis six times per week versus three times per week. *N Engl J Med*. 2010;363:2287-2300.
45. Tennankore KK, Na Y, Wald R, Chan CT, Perl J. Short daily-, nocturnal- and conventional-home hemodialysis have similar patient and treatment survival. *Kidney Int*. 2017.
46. Chan CT, Floras JS, Miller JA, Richardson RM, Pierratos A. Regression of left ventricular hypertrophy after conversion to nocturnal hemodialysis. *Kidney Int*. 2002;61:2235-9.
47. Lockridge RS, Jr., Spencer M, Craft V, et al. Nightly home hemodialysis: five and one-half years of experience in Lynchburg, Virginia. *Hemodial Int*. 2004;8:61-9.
48. Nesrallah G, Suri R, Moist L, Kortas C, Lindsay RM. Volume control and blood pressure management in patients undergoing quotidian hemodialysis. *Am J Kidney Dis*. 2003;42:13-7.
49. Kraus M, Burkart J, Hegeman R, Solomon R, Coplon N, Moran J. A comparison of center-based vs. home-based daily hemodialysis for patients with end-stage renal disease. *Hemodial Int*. 2007;11:468-77.
50. McGregor DO, Buttmore AL, Lynn KL, Nicholls MG, Jardine DL. A Comparative Study of Blood Pressure Control with Short In-Center versus Long Home Hemodialysis. *Blood Purif*. 2001;19:293-300.
51. Chan CT, Harvey PJ, Picton P, Pierratos A, Miller JA, Floras JS. Short-term blood pressure, noradrenergic, and vascular effects of nocturnal home hemodialysis. *Hypertension*. 2003;42:925-31.
52. Chazot C, Charra B, Laurent G, et al. Interdialysis blood pressure control by long haemodialysis sessions. *Nephrol Dial Transplant*. 1995;10:831-7.
53. Fagugli RM, Reboldi G, Quintaliani G, et al. Short daily hemodialysis: blood pressure control and left ventricular mass reduction in hypertensive hemodialysis patients. *Am J Kidney Dis*. 2001;38:371-6.

54. Culleton BF, Walsh M, Klarenbach SW, et al. Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. *JAMA*. 2007;298:1291-9.
55. McCullough PA, Chan CT, Weinhandl ED, Burkart JM, Bakris GL. Intensive Hemodialysis, Left Ventricular Hypertrophy, and Cardiovascular Disease. *Am J Kidney Dis*. 2016;68:55-S14.
56. Susantitaphong P, Koulouridis I, Balk EM, Madias NE, Jaber BL. Effect of frequent or extended hemodialysis on cardiovascular parameters: a meta-analysis. *Am J Kidney Dis*. 2012;59:689-99.
57. Jefferies HJ, Virk B, Schiller B, Moran J, McIntyre CW. Frequent hemodialysis schedules are associated with reduced levels of dialysis-induced cardiac injury (myocardial stunning). *Clin J Am Soc Nephrol*. 2011;6:1326-32.
58. Cornelis T, van der Sande FM, Eloit S, et al. Acute hemodynamic response and uremic toxin removal in conventional and extended hemodialysis and hemodiafiltration: a randomized crossover study. *Am J Kidney Dis*. 2014;64:247-56.
59. Thomson BK, Momciu B, Huang SH, et al. Frequent nocturnal hemodialysis associates with improvement of prolonged QTc intervals. *Nephron Clin Pract*. 2013;123:74-82.
60. Thomson BK, Huang SH, Chan C, Urquhart B, Skanes A, Lindsay RM. Nocturnal home hemodialysis associates with improvement of electrocardiographic features linked to sudden cardiac death. *ASAIO J*. 2014;60:99-105.
61. Brunelli SM, Du MC, Oestreicher N, Rakov V, Spiegel DM. Serum Potassium and Short-term Clinical Outcomes Among Hemodialysis Patients: Impact of the Long Interdialytic Interval. *Am J Kidney Dis*. 2017;70:21-9.
62. Roy-Chaudhury P, Tumlin JA, Koplan BA, et al. Primary outcomes of the Monitoring in Dialysis Study indicate that clinically significant arrhythmias are common in hemodialysis patients and related to dialytic cycle. *Kidney Int*. 2018;93:941-51.
63. Tsilonis K, Sarafidis PA, Kamperidis V, et al. Echocardiographic Parameters During Long and Short Interdialytic Intervals in Hemodialysis Patients. *Am J Kidney Dis*. 2016;68:772-81.
64. Foley RN, Gilbertson DT, Murray T, Collins AJ. Long interdialytic interval and mortality among patients receiving hemodialysis. *N Engl J Med*. 2011;365:1099-107.
65. Krishnasamy R, Badve SV, Hawley CM, et al. Daily variation in death in patients treated by long-term dialysis: comparison of in-center hemodialysis to peritoneal and home hemodialysis. *Am J Kidney Dis*. 2013;61:96-103.
66. Zhang H, Schaubel DE, Kalbfleisch JD, et al. Dialysis outcomes and analysis of practice patterns suggests the dialysis schedule affects day-of-week mortality. *Kidney Int*. 2012;81:1108-15.
67. Bleyer AJ, Russell GB, Satko SG. Sudden and cardiac death rates in hemodialysis patients. *Kidney Int*. 1999;55:1553-9.
68. Fotheringham J, Fogarty DG, El NM, Campbell MJ, Farrington K. The mortality and hospitalization rates associated with the long interdialytic gap in thrice-weekly hemodialysis patients. *Kidney Int*. 2015;88:569-75.
69. Karnik JA, Young BS, Lew NL, et al. Cardiac arrest and sudden death in dialysis units. *Kidney Int*. 2001;60:350-7.
70. Weinhandl ED, Nieman KM, Gilbertson DT, Collins AJ. Hospitalization in daily home hemodialysis and matched thrice-weekly in-center hemodialysis patients. *Am J Kidney Dis*. 2015;65:98-108.
71. Walsh M, Manns BJ, Klarenbach S, Tonelli M, Hemmelgarn B, Culleton B. The effects of nocturnal compared with conventional hemodialysis on mineral metabolism: A randomized-controlled trial. *Hemodial Int*. 2010;14:174-81.
72. Ebah LM, Akhtar M, Wilde I, et al. Phosphate enrichment of dialysate for use in standard and extended haemodialysis. *Blood Purif*. 2012;34:28-33.
73. Jansz TT, Verhaar MC, London GM, van Jaarsveld BC. Is progression of coronary artery calcification influenced by modality of renal replacement therapy? A systematic review. *Clin Kidney J*. In press.
74. Macdougall IC. Intravenous iron therapy in patients with chronic kidney disease: recent evidence and future directions. *Clin Kidney J*. 2017;10:i16-i24.
75. Chan CT, Liu PP, Arab S, Jamal N, Messner HA. Nocturnal hemodialysis improves erythropoietin responsiveness and growth of hematopoietic stem cells. *J Am Soc Nephrol*. 2009;20:665-71.
76. Poon CK, Tang HL, Wong JH, et al. Effect of alternate night nocturnal home hemodialysis on anemia control in patients with end-stage renal disease. *Hemodial Int*. 2015;19:235-41.
77. Schwartz DI, Pierratos A, Richardson RM, Fenton SS, Chan CT. Impact of nocturnal home hemodialysis on anemia management in patients with end-stage renal disease. *Clin Nephrol*. 2005;63:202-8.
78. Jansz TT, Özyilmaz A, Grooteman MPC, et al. Long-term clinical parameters after switching to nocturnal haemodialysis: a Dutch propensity-score-matched cohort study comparing patients on nocturnal haemodialysis with patients on 3-times weekly haemodialysis/haemodiafiltration. *BMJ Open*. 2017-019900.R1. In press.
79. Shepshelovich D, Rozen-Zvi B, Avni T, Gafer U, Gafer-Gvili A. Intravenous Versus Oral Iron Supplementation for the Treatment of Anemia in CKD: An Updated Systematic Review and Meta-analysis. *Am J Kidney Dis*. 2016;68:677-90.
80. KDIGO Clinical Practical Guideline for Anemia in Chronic Kidney Disease 2012 [Internet]. (cited 1 March 2018). Available from: http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-Anemia%20GL.pdf.
81. Addendum van de richtlijn renale anemie 2014 van de NFN [Internet]. (cited 1 March 2018). Available from: <https://www.nefro.nl/sites/www.nefro.nl/files/richtlijnen/Veldnorm%20iv%20ijzerbehandeling%3B%2021-12-2015.%20Addendum%20voor%20de%20Richtlijn%20renale%20anemie%20van%20de%20NFN.pdf>
82. Okundaye I, Abrinko P, Hou S. Registry of pregnancy in dialysis patients. *Am J Kidney Dis*. 1998;31:766-73.
83. Asamiya Y, Otsubo S, Matsuda Y, et al. The importance of low blood urea nitrogen levels in pregnant patients undergoing hemodialysis to optimize birth weight and gestational age. *Kidney Int*. 2009;75:1217-22.
84. Barua M, Hladunewich M, Keunen J, et al. Successful pregnancies on nocturnal home hemodialysis. *Clin J Am Soc Nephrol*. 2008;3:392-6.
85. Hladunewich MA, Hou S, Odutayo A, et al. Intensive hemodialysis associates with improved pregnancy outcomes: a Canadian and United States cohort comparison. *J Am Soc Nephrol*. 2014;25:1103-9.
86. Piccoli GB, Minelli F, Versino E, et al. Pregnancy in dialysis patients in the new millennium: a systematic review and meta-regression analysis correlating dialysis schedules and pregnancy outcomes. *Nephrol Dial Transplant*. 2016;31:1915-34.
87. Van Eps C, Hawley C, Jeffries J, et al. Changes in serum prolactin, sex hormones and thyroid function with alternate nightly nocturnal home haemodialysis. *Nephrology (Carlton)*. 2012;17:42-7.
88. Van Eps CL, Jeffries JK, Johnson DW, et al. Quality of life and alternate nightly nocturnal home hemodialysis. *Hemodial Int*. 2010;14:29-38.
89. Vos PF, Zilch O, Jennekens-Schinkel A, et al. Effect of short daily home haemodialysis on quality of life, cognitive functioning and the electroencephalogram. *Nephrol Dial Transplant*. 2006;21:2529-35.
90. Heidenheim AP, Muirhead N, Moist L, Lindsay RM. Patient quality of life on quotidian hemodialysis. *Am J Kidney Dis*. 2003;42:36-41.
91. Jaber BL, Lee Y, Collins AJ, et al. Effect of daily hemodialysis on depressive symptoms and postdialysis recovery time: interim report from the FREEDOM (Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements) Study. *Am J Kidney Dis*. 2010;56:531-9.
92. Jaber BL, Schiller B, Burkart JM, et al. Impact of short daily hemodialysis on restless legs symptoms and sleep disturbances. *Clin J Am Soc Nephrol*. 2011;6:1049-56.
93. Hanly PJ, Pierratos A. Improvement of sleep apnea in patients with chronic renal failure who undergo nocturnal hemodialysis. *N Engl J Med*. 2001;344:102-7.
94. Tordoir J, Canaud B, Haage P, et al. EBPG on Vascular Access. *Nephrol Dial Transplant*. 2007;22 Suppl 2:i188-117.
95. Cafazzo JA, Leonard K, Easty AC, Rossos PG, Chan CT. Patient-perceived barriers to the adoption of nocturnal home hemodialysis. *Clin J Am Soc Nephrol*. 2009;4:784-9.
96. Moist LM, Trpeski L, Na Y, Lok CE. Increased hemodialysis catheter use in Canada and associated mortality risk: data from the Canadian Organ Replacement Registry 2001-2004. *Clin J Am Soc Nephrol*. 2008;3:1726-32.

97. Perl J, Nessim SJ, Moist LM, et al. Vascular Access Type and Patient and Technique Survival in Home Hemodialysis Patients: The Canadian Organ Replacement Register. *Am J Kidney Dis.* 2016;67:251-9.
98. Rivara MB, Soohoo M, Streja E, et al. Association of Vascular Access Type with Mortality, Hospitalization, and Transfer to In-Center Hemodialysis in Patients Undergoing Home Hemodialysis. *Clin J Am Soc Nephrol.* 2016;11:298-307.
99. Mustafa RA, Zimmerman D, Rioux JP, et al. Vascular access for intensive maintenance hemodialysis: a systematic review for a Canadian Society of Nephrology clinical practice guideline. *Am J Kidney Dis.* 2013;62:112-31.
100. Tordoir JH, Bode AS, van Loon MM. Preferred strategy for hemodialysis access creation in elderly patients. *Eur J Vasc Endovasc Surg.* 2015;49:738-43.
101. Hall RK, Myers ER, Rosas SE, O'Hare AM, Colon-Emeric CS. Choice of Hemodialysis Access in Older Adults: A Cost-Effectiveness Analysis. *Clin J Am Soc Nephrol.* 2017;12:947-54.
102. Mott. Overcoming a key barrier to home dialysis. The art of teaching buttonhole self-cannulation [Internet]. 2011 (cited 2 September 2017). Available from: <http://homodialysis.org/documents/pros/ButtonholeCannulation.pdf>
103. Twardowski Z, Lebek R, Kubara H. Six-year experience with the creation and use of internal arteriovenous fistulae in patients treated with repeated hemodialysis [in Polish]. *Pol Arch Med Wewn.* 1977; 57: 205-14.
104. Verhallen AM, Kooistra MP, van Jaarsveld BC. Cannulating in haemodialysis: rope-ladder or buttonhole technique? *Nephrol Dial Transplant.* 2007;22:2601-4.
105. Wong B, Muneer M, Wiebe N, et al. Buttonhole versus rope-ladder cannulation of arteriovenous fistulas for hemodialysis: a systematic review. *Am J Kidney Dis.* 2014;64:918-36.
106. Van Loon MM, Goovaerts T, Kessels AG, van der Sande FM, Tordoir JH. Buttonhole needling of haemodialysis arteriovenous fistulae results in less complications and interventions compared to the rope-ladder technique. *Nephrol Dial Transplant.* 2010;25:225-30.
107. Vaux E, King J, Lloyd S, et al. Effect of buttonhole cannulation with a polycarbonate PEG on in-center hemodialysis fistula outcomes: a randomized controlled trial. *Am J Kidney Dis.* 2013;62:81-8.
108. Muir CA, Kotwal SS, Hawley CM, et al. Buttonhole cannulation and clinical outcomes in a home hemodialysis cohort and systematic review. *Clin J Am Soc Nephrol.* 2014;9:110-9.
109. NfN richtlijn Preventie, diagnostiek en behandeling van toegangerelateerde infecties bij hemodialyse [Internet]. 2016 (cited 17 November 2017). Available from: <https://www.nfro.nl/richtlijnen>.
110. Bosman PJ, Boereboom FT, Smits HF, Eikelboom BC, Koomans HA, Blankestijn PJ. Pressure or flow recordings for the surveillance of hemodialysis grafts. *Kidney Int.* 1997;52:1084-8.
111. Smits JH, van der Linden J, Hagen EC, et al. Graft surveillance: venous pressure, access flow, or the combination? *Kidney Int.* 2001;59:1551-8.
112. Verhallen A. Successful vascular access management for home haemodialysis: a practical approach. *J Ren Care.* 2013;39 Suppl 1:28-34.
113. Faratro R, Jeffries J, Nesrallah GE, MacRae JM. The care and keeping of vascular access for home hemodialysis patients. *Hemodial Int.* 2015;19 Suppl 1:S80-S92.
114. Suri RS, Larive B, Sherer S, et al. Risk of vascular access complications with frequent hemodialysis. *J Am Soc Nephrol.* 2013;24:498-505.
115. Perl J, Lok CE, Chan CT. Central venous catheter outcomes in nocturnal hemodialysis. *Kidney Int.* 2006;70:1348-54.
116. Van Eps CL, Jones M, Ng T, et al. The impact of extended-hours home hemodialysis and buttonhole cannulation technique on hospitalization rates for septic events related to dialysis access. *Hemodial Int.* 2010;14:451-63.
117. Kjellstrand CM, Blagg CR, Twardowski ZJ, Bower J. Blood access and daily hemodialysis: clinical experience and review of the literature. *ASAIO J.* 2003;49:645-9.
118. Pinciaroli AR. Results of Daily Hemodialysis in Catanzaro: 12-Year Experience With 22 Patients Treated For More Than One Year. *Home Hemodial Int (1997).* 1998;2:12-7.
119. Quintaliani G, Buoncristiani U, Fagugli R, et al. Survival of vascular access during daily and three times a week hemodialysis. *Clin Nephrol.* 2000;53:372-7.
120. Cornelis T, Usvyat LA, Tordoir JH, et al. Vascular access vulnerability in intensive hemodialysis: a significant Achilles' heel? *Blood Purif.* 2014;37:222-8.
121. Kooistra MP, Vos PF. Daily Home Hemodialysis: Towards a More Physiological Treatment of Patients with ESRD. *Seminars in Dialysis* 1999;12:424-30.
122. Tennankore KK, d'Gama C, Faratro R, Fung S, Wong E, Chan CT. Adverse technical events in home hemodialysis. *Am J Kidney Dis.* 2015;65:116-21.
123. Wong B, Zimmerman D, Reintjes F, et al. Procedure-related serious adverse events among home hemodialysis patients: a quality assurance perspective. *Am J Kidney Dis.* 2014;63:251-8.
124. Sands JJ, Lacson E Jr, Ofsthun NJ, Kay JC, Diaz-Buxo JA. Home hemodialysis: a comparison of in-center and home hemodialysis therapy in a cohort of successful home hemodialysis patients. *ASAIO J.* 2009;55:361-8.
125. Hawley CM, Jeffries J, Nearhos J, van EC. Complications of home hemodialysis. *Hemodial Int.* 2008;12 Suppl 1:S21-S25.
126. Ludlow MJ, George CR, Hawley CM, et al. How Australian nephrologists view home dialysis: results of a national survey. *Nephrology (Carlton).* 2011;16:446-52.
127. Jayanti A, Morris J, Stenvinkel P, Mitra S. Home hemodialysis: beliefs, attitudes, and practice patterns. *Hemodial Int.* 2014;18:767-76.
128. Fluck RJ, Fouque D, Lockridge RS, Jr. Nephrologists' perspectives on dialysis treatment: results of an international survey. *BMC Nephrol.* 2014;15:16.
129. Mendelssohn DC, Mullaney SR, Jung B, Blake PG, Mehta RL. What do American nephrologists think about dialysis modality selection? *Am J Kidney Dis.* 2001;37:22-29.
130. Jung B, Blake PG, Mehta RL, Mendelssohn DC. Attitudes of Canadian nephrologists toward dialysis modality selection. *Perit Dial Int.* 1999;19:263-8.
131. Ledebro I. What limits the expansion of self-care dialysis at home? *Hemodial Int.* 2008;12 Suppl 1:S55-S60.
132. Pipkin M, Eggers PW, Larive B, et al. Recruitment and training for home hemodialysis: experience and lessons from the Nocturnal Dialysis Trial. *Clin J Am Soc Nephrol.* 2010;5:1614-20.
133. Walker RC, Hanson CS, Palmer SC, et al. Patient and caregiver perspectives on home hemodialysis: a systematic review. *Am J Kidney Dis.* 2015;65:451-63.
134. Suri RS, Larive B, Garg AX, et al. Burden on caregivers as perceived by hemodialysis patients in the Frequent Hemodialysis Network (FHN) trials. *Nephrol Dial Transplant.* 2011;26:2316-22.
135. Suri RS, Larive B, Hall Y, et al. Effects of frequent hemodialysis on perceived caregiver burden in the Frequent Hemodialysis Network trials. *Clin J Am Soc Nephrol.* 2014;9:936-42.
136. McLaughlin K, Manns B, Mortis G, Hons R, Taub K. Why patients with ESRD do not select self-care dialysis as a treatment option. *Am J Kidney Dis.* 2003;41:380-5.
137. Walker RC, Hanson CS, Palmer SC, et al. Patient and caregiver perspectives on home hemodialysis: a systematic review. *Am J Kidney Dis.* 2015;65:451-63.
138. Mehrotra R, Marsh D, Vonesh E, Peters V, Nissenson A. Patient education and access of ESRD patients to renal replacement therapies beyond in-center hemodialysis. *Kidney Int.* 2005;68:378-90.
139. Tong A, Palmer S, Manns B, et al. The beliefs and expectations of patients and caregivers about home haemodialysis: an interview study. *BMJ Open.* 2013;3.
140. Elizabeth J L, Hanna L, Walker D, et al. Pre-dialysis education and patient choice. *J Ren Care.* 2006;32:214-20.
141. Agraharkar M, Barclay C, Agraharkar A. Staff-assisted home hemodialysis in debilitated or terminally ill patients. *Int Urol Nephrol.* 2002;33:139-44.
142. Reddy NC, Korbet SM, Wozniak JA, Floramo SL, Lewis EJ. Staff-assisted nursing home haemodialysis: patient characteristics and outcomes. *Nephrol Dial Transplant.* 2007;22:1399-406.
143. Cafazzo JA, Leonard K, Easty AC, Rossos PG, Chan CT. Patient perceptions of remote monitoring for nocturnal home hemodialysis. *Hemodial Int.* 2010;14:471-7.

144. Lehoux P. Patients' perspectives on high-tech home care: a qualitative inquiry into the user-friendliness of four technologies. *BMC Health Serv Res.* 2004;4:28.
145. Physidia human solutions [Internet]. (cited 23 October 2017). Available from: <http://www.physidia.fr>.
146. Nxstage [Internet]. (cited 23 October 2017). Available from: <http://www.nxstage.com>.
147. Quanta SC+ [Internet]. (cited 25 September 2017). Available from: <http://www.quantadt.com/>.
148. Neokidney [Internet]. (cited 25 September 2017). Available from: <http://neokidney.nl>.
149. Lockridge RS. ASN Kidney News: Technical Advances in Home Hemodialysis [Internet]. 2014 (cited 25 September 2017). Available from: <http://www.kidneynews.org/kidney-news/special-sections/home-dialysis/technical-advances-in-home-hemodialysis>.
150. Medtronic Inc. Patent: US 20150250937A1. Multi-use sorbent cartridge. (cited 1 November 2017). Available from: <https://www.google.com/patents/US20150250937>.
151. Kooman JP, Joles JA, Gerritsen KG. Creating a wearable artificial kidney: where are we now? *Expert Rev Med Devices.* 2015;12:373-6.
152. Gura V, Rivara MB, Bieber S, et al. A wearable artificial kidney for patients with end-stage renal disease. *JCI Insight.* 2016;1.
153. Eisen MS. Patent: US8220643B2. 2012 (cited 25 September 2017). Available from: <https://patents.google.com/patent/US8220643B2/en>.
154. Wester M, Simonis F, Lachkar N, et al. Removal of urea in a wearable dialysis device: a reappraisal of electro-oxidation. *Artif Organs.* 2014;38:998-1006.
155. Liu N, Kim J, Jung Y, et al. Remote Monitoring Systems for Chronic Patients on Home Hemodialysis: Field Test of a Copresence-Enhanced Design. *JMIR Hum Factors.* 2017;4:e21.
156. Ditchburn JL, Marshall A. Renal telemedicine through video-as-a-service delivered to patients on home dialysis: A qualitative study on the renal care team members' experience. *J Ren Care.* 2017;43:175-82.